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CLINICAL INVESTIGATION

A simulation study on transcellular fluid shifts induced by hemodialysis

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A simulation study on transcellular fluid shifts induced by hemodialysis. A computer-based model has been developed to predict the changes in serum sodium, urea concentration, and osmolality as well as transcellular fluid distribution which occur during hemodialysis. Sodium and urea transfers across the dialyzer membrane and transcellular fluid shifts in response to the sodium transfer were modeled assuming that only sodium and its accompanying anions are important as effective osmotic substances in extracellular fluid. Model predictions were consistent with values measured in five patients who were studied on hemodialysis at three different dialysate sodium concentrations equal to 7% below and 7% above the predialysis serum concentration. The measurements and model predictions indicate that serum sodium concentration decreases and intracellular fluid volume increases in dialyses with dialysate Na^+ concentration used in conventional hemodialysis, whereas serum sodium concentration increases and intracellular volume decreases in high sodium dialyses. An analysis of model predictions indicates that a reasonable estimation of total body water and the intracellular to extracellular volume ratio enables us to accurately predict the magnitude of transcellular fluid shifts induced by hemodialysis as well as the postdialysis serum sodium concentration and osmolality.

Une étude en simulation des transferts transcellulaires de fluides induits par l'hémodialyse. Un modèle assisté par ordinateur a été développé pour prédire les modifications du sodium, de la concentration uréique, et de l'osmolalité sérique, et de la distribution transcellulaire de fluides qui surviennent pendant l'hémodialyse. Les transferts de sodium et d'urée à travers la membrane du dialyseur et les déplacements transcellulaires de fluides en réponse au transfert de sodium ont été modélisés en supposant que seul le sodium et ses anions accompagnateurs sont importants en tant que substances osmotiquement efficaces dans le fluide extracellulaire. Les prédictions du modèle étaient en accord avec les valeurs mesurées chez cinq malades qui ont été étudiés en hémodialyse avec trois différentes concentrations du sodium dans le dialysat, égale, 7% inférieure ou 7% supérieure à la concentration sérique avant dialyse. Les mesures et les prédictions du modèle indiquent que la concentration de sodium sérique diminue et que le volume de fluide intracellulaire augmente lors des dialyses avec la concentration de Na^+ dans le dialysat utilisée dans l'hemodialyse conventionnelle, tandis que la concentration de sodium sérique augmente et que le volume intracellulaire diminue lors des dialyses avec sodium élevé. Une analyse des prédictions du modèle indique qu'une estimation raissonable de l'eau totale de l'organisme et du rapport du volume intracellulaire sur le volume extracellulaire nous permet de prévoir de façon précise l'importance des transferts transcellulaires de fluides induits par l'hémodialyse, ainsi que la concentration de sodium et l'osmolalité sériques postdialytiques.

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It has been demonstrated that the use of dialysate with a high Na^+ concentration reduces the incidence of hypotension [1], disequilibrium syndrome [1, 2], and muscle cramps [1, 3] during hemodialysis. The reasons for this reduction in symptoms are not well understood, but may be related to differences in body fluid distribution between the intracellular and extracellular fluid compartments [1–4]. In the present study, measured intracellular and extracellular fluid volumes as well as serum Na^+ concentration and osmolality before and after hemodialsyis at three different dialysate Na^+ concentrations were compared to values predicted by a computerized model that simulates transcellular fluid shifts during hemodialysis related to the sodium transfer across the dialyzer membrane. The model predictions were found to agree very well with the measured values. The measurements and model predictions show that high Na^+ hemodialysis allows fluid removal from both the intracellular and extracellular fluid compartments, whereas with the Na^+ concentration used in conventional hemodialysis, fluid is removed from the extracellular compartment only. Since the clinical validity of the model has been confirmed by the agreement of the predictions with measured values of postdialysis serum Na^+ concentration and osmolality as well as the magnitude of transcellular fluid shifts induced by hemodialysis, the model permits a more complete quantitative analysis of sodium and water metabolism in dialysis patients. By employing the principles described in the present study, it is possible to utilize high Na^+ dialysate without inducing long-term positive sodium and fluid balance.

Methods

Applying a well established principle [5] governing transcellular fluid dynamics to hemodialysis (HD) therapy, a computer-based model [6] was developed to predict the changes in serum [Na^+], blood urea nitrogen concentration (BUN), plasma osmolality (P_{Osm}), and transcellular fluid distribution which occur during HD. Only sodium and its accompanying anions were considered important as effective osmotic substances in extracellular fluid to induce transcellular fluid shifts, and urea was assumed freely permeable across cell membranes. The detailed formulations are described in the **Appendix.**

Five stable chronic HD patients (two males and three females; mean age, 49; range, 24 to 71 years) were studied. The patients were admitted to the Clinical Research Center at the

University of Missouri Hospital and Clinics, Columbia, Missouri, in the evening prior to each study dialysis. Patients were weighed upon admission, and if their weight was less than 2 kg above their estimated ideal weight, they were given additional fluids in the form of soup containing 100 mEq/liter of sodium. Each patient underwent three study dialyses which differed only in the sodium chloride concentration of the dialysate. The patients were admitted separately for each of the three study dialyses, and each study dialysis were separated by at least two regular HD treatments. The order of study dialyses was randomly determined. The dialysate sodium concentration was adjusted on the basis of the predialysis serum $[Na^+]$ by adding 2.5 mEq/ml of sodium chloride to the basic dialysate. The normal Na^+ dialysate contained a dialysate Na^+ concentration equal to the patient's predialysis serum $[Na^+]$ while the low Na^+ dialysate and high Na^+ dialysate contained Na^+ concentrations which were 7% less and 7% greater than the predialysis serum $[Na^+]$, respectively. The basic dialysate contained 130 mEq/liter of Na^+, 2 mEq/liter of K^+, 3.25 mEq/liter of Ca^{++}, 1.5 mEq/liter of Mg^{++}, 102 mEq/liter of Cl^-, 35 mEq/liter of CH_3COO^- and 200 mg/dl of glucose. The dialysate flow rate was always 500 ml/min. Mean values of the extracorporeal blood flow rate (Q_B), the hematocrit (Hct) and the dialyzer urea clearance (K_{urea}) are listed in Table 1 for the three study groups. K_{urea} was extrapolated from in vivo clearances measured on the same types of dialyzers in other patients at a zero ultrafiltration rate. Immediately prior to the dialysis treatment, serum $[Na^+]$, BUN, and P_{Osm} were measured. Total body fluid volume (TBF) and extracellular fluid volume (ECF) were also determined before dialysis simultaneously using ^3H_2O and $Na_2{}^{35}SO_4$, respectively [7]. Patients were kept in a supine position until these studies were completed. A 4-hr HD was then performed in a bed with a metabolic scale. During the dialysis treatment, fluid was removed at a constant rate of 0.5 kg/hr, and serum $[Na^+]$ was determined every hour. After the dialysis procedure, BUN, P_{Osm}, and ECF were again determined, assuming that no transcellular fluid shifts occurred following the dialysis procedure. Postdialysis TBF was obtained assuming that changes in TBF were equal to the changes in body weight. ICF was calculated as the difference between TBF and ECF. It should be noted that 200 to 700 ml of 0.9% (w/v) NaCl were infused in four of five patients who developed symptomatic hypotension during low Na^+ HD. The detailed methods for body fluid volume determination and their variability are described elsewhere [7, 8].

Results were expressed in terms of the mean ± SEM, and the significance of the difference between pre- and postdialysis values was tested by the Student's *t* test for paired samples. This test was also used for comparing measured postdialysis values with the model predictions.

Results

Validity of model assumptions

As described in detail in the **Appendix,** firstly, water is assumed freely permeable to cell membranes. Therefore, effective osmolality should be equal in both intra- and extracellular compartments across the cell membrane every moment.

$$C_I(t) = C_E(t) \qquad (1)$$

Table 1. Conditions of dialysis for the three study groups[a]

Group	Dialysate Na^+ *mEq/liter*	Q_B *ml/min*	Hct *%*	K_{urea} *ml/min*
Normal Na^+ HD	141 ± 2	212 ± 6	23.1 ± 3.7	169 ± 10
Low Na^+ HD	131 ± 1	215 ± 6	23.5 ± 2.9	171 ± 10
High Na^+ HD	150 ± 2	215 ± 6	22.0 ± 3.2	176 ± 11

[a] Results are expressed as mean ± SEM (N = 5) in each group.

Table 2. Amount of intracellular effective osmotic cations before and after hemodialysis[a]

Group	Before HD	Significance	After HD
Normal Na^+ HD	3860 ± 320	NS	3820 ± 330
Low Na^+ HD	3750 ± 350	NS	3660 ± 320
High Na^+ HD	3610 ± 280	NS	3600 ± 290

[a] Results are expressed as mean ± SEM (N = 5) in the unit of mEq in each group. The significance of the difference is based on a paired *t* test.

Where $C_I(t)$ and $C_E(t)$ are the intra- and extracellular effective osmolality at time t, respectively.

Secondly, we assumed that only sodium and its accompanying anions are important as effective osmotic substances in the extracellular compartment.

$$C_E(t) = k \times [Na^+(t)] \times \frac{R_D}{F_W} \qquad (2)$$

where k, $[Na^+(t)]$, R_D, and F_W are the osmotic coefficient for sodium chloride, serum sodium concentration at time t, the Gibbs-Donnan ratio, and the correction factor for the exclusion volume of plasma protein, respectively, and $[Na^+(t)] \times R_D/F_W$ corresponds to the sodium concentration in the interstitial fluid. Although sodium and urea are the major osmotic substances in the extracellular fluid in uremic patients, only sodium and its accompanying anions are considered important in osmotically induced transcellular fluid shifts.

Thirdly, since the effective osmotic substances do not move across the cell membrane, the absolute amount of effective osmotic substances in the cell is assumed constant.

$$ICF(t) \times C_I(t) = ICF(t + \Delta t) \times C_I(t + \Delta t) \qquad (3)$$

where ICF(t) is the intracellular fluid volume at time t.

Solving equations *(1)* to *(3)*, these assumptions are expressed simply as follows:

$$ICF(t) \times [Na^+(t)] = ICF(t + \Delta t) \times [Na^+(t + \Delta t)] \qquad (4)$$

This equation is a well known principle [5] governing transcellular fluid distribution and means that the absolute amount of intracellular effective osmotic cations is constant. Since we measured the intracellular fluid volume and serum Na^+ concentration before and after hemodialysis, the validity of assumptions underlying our model can be directly confirmed in the present experimental situations. As shown in Table 2, there was no significant difference in the absolute amount of intracellular effective osmotic cations between before and after hemodialysis in any group, suggesting the validity of application of the well known principle [5] to hemodialysis therapy.

Table 3. Serum Na^+ concentrations and body fluid volumes before and after hemodialysis[a]

Group	Parameters	Before HD		After HD		
		Measured	Significance	Measured	Significance	Model prediction
Normal Na^+ HD	Serum $[Na^+]$, *mEq/liter*	140 ± 2	NS	138 ± 1	NS	138 ± 1
	ICF, *liters*	27.6 ± 2.4	NS	27.8 ± 2.5	NS	27.9 ± 2.4
	ECF, *liters*	16.2 ± 1.6	$P < 0.02$	14.0 ± 1.2	NS	13.8 ± 1.5
Low Na^+ HD	Serum $[Na^+]$, *mEq/liter*	139 ± 1	$P < 0.05$	134 ± 2	NS	132 ± 1
	ICF, *liters*	27.0 ± 2.5	NS	27.4 ± 2.5	$P < 0.02$	28.4 ± 2.6
	ECF, *liters*	15.8 ± 1.4	$P < 0.001$	13.5 ± 1.4	$P < 0.02$	12.5 ± 1.5
High Na^+ HD	Serum $[Na^+]$, *mEq/liter*	140 ± 1	$P < 0.02$	145 ± 2	NS	144 ± 2
	ICF, *liters*	25.9 ± 2.1	NS	24.9 ± 2.0	NS	25.1 ± 1.9
	ECF, *liters*	16.5 ± 1.8	NS	15.8 ± 1.6	NS	15.5 ± 1.8

[a] Results are expressed as mean ± SEM ($N = 5$) in each group. The significance of differences is based on a paired t test.

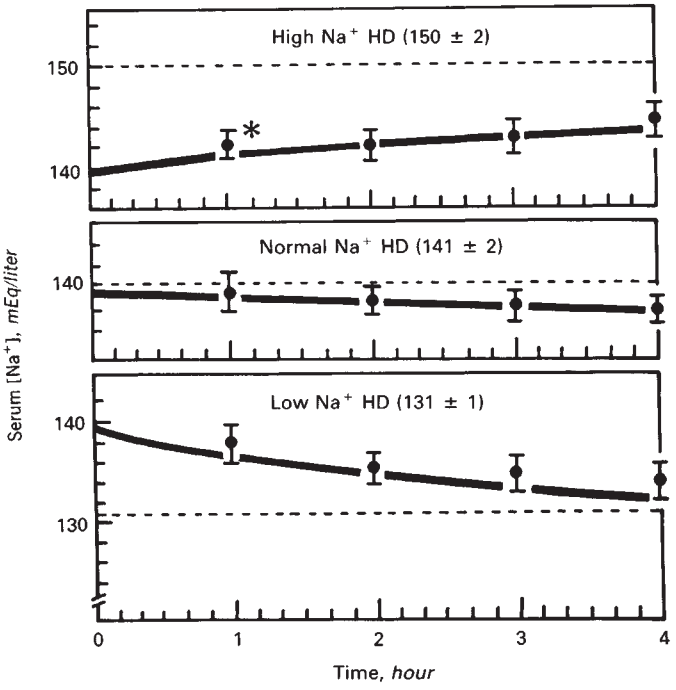

Fig. 1. *Serum $[Na^+]$ as a function of time during hemodialysis.* The *plotted points* are the measured values (mean ± SEM), and the *solid line* is the computer prediction. The mean dialysate Na^+ concentrations used for each group are also plotted as a *broken line*. The significance of the differences between measured and predicted serum $[Na^+]$ was tested by the paired t test. The *asterisk* represents $P < 0.005$.

Comparison of model predictions with experimental measurements

Mean pre- and postdialysis values of serum $[Na^+]$ and body fluid volumes that were experimentally measured, and the mean postdialysis values predicted by the computer model are summarized in Table 3 for the normal, low, and high dialysate Na^+ dialyses. For those patients with normal and high dialysate Na^+, the experimentally determined values of serum $[Na^+]$ and body fluid volumes are in excellent agreement with the model predictions. For those patients with low dialysate Na^+, there is no significant difference between the measured and predicted serum $[Na^+]$ values, but the measured and predicted values of body fluid volumes are different at the $P = 0.02$ level of significance. The model predicts an intracellular fluid shift larger than experimentally measured.

Figure 1 is a plot of the time course of mean serum $[Na^+]$ during dialysis with the normal, low and high dialysate Na^+ concentrations. The lines shown are computer-predicted, and the plotted points are the measured values. There was an excellent agreement between the measured and predicted values. The only significant difference was seen in the value at 1 hr after the beginning of the high Na^+ hemodialysis. Serum $[Na^+]$ levels are relatively unchanged with the normal dialysate Na^+ concentration, but increase significantly with the high Na^+ dialysate, and decrease significantly with the low Na^+ dialysate. With the normal dialysate Na^+ concentration, there is little change in intracellular volume, and the ultrafiltered fluid is removed mainly from the extracellular compartment. With a high Na^+ dialysate concentration, the intracellular compartment also contributes to the fluid removal, so that there is less shrinkage of the extracellular fluid volume. With the low Na^+ dialysate concentration, not only does the extracellular fluid volume shrink due to ultrafiltration, but in addition, there is an intracellular fluid shift so that the intracellular compartment is expanded by the dialysis procedure.

Measured and predicted BUN and P_{Osm} levels are compared in Table 4. The predicted postdialysis values agree well with the measured values. The fall in BUN levels pre- to postdialysis is comparable in the three groups. The osmolality decrease is smallest in the patients exhibiting high dialysate Na^+, expanding with the normal Na^+ dialysis, and being greatest in the low Na^+ dialysis. This is related to the direction of the change in serum $[Na^+]$ as shown in Table 3 and Figure 1.

Effects of sodium concentration gradient across the dialyzer membrane

The change in serum sodium concentration ($\Delta[Na^+]$) was estimated based on our computer model as a function of the sodium concentration gradient ($\Delta D_{Na}+$) between dialysate and serum (predialysis), and depicted in Figure 2A together with measured values. There was no significant difference between the estimated and measured values. The trend is linear with a non-zero intercept on the X-axis. The non-zero X-intercept is

Table 4. BUN and P_{Osm} before and after hemodialysis[a]

Group	Parameters	Before HD		After HD		
		Measured	Significance	Measured	Significance	Model prediction
Normal Na^+ HD	BUN, *mg/dl*	16 ± 12	$P < 0.02$	30 ± 9	NS	30 ± 9
	P_{Osm}, *mOsm/kg* H_2O	307 ± 7	$P < 0.05$	290 ± 3	NS	293 ± 4
Low Na^+ HD	BUN, *mg/dl*	57 ± 5	$P < 0.001$	24 ± 3	NS	22 ± 2
	P_{Osm}, *mOsm/kg* H_2O	309 ± 7	$P < 0.001$	281 ± 6	NS	281 ± 8
High Na^+ HD	BUN, *mg/dl*	67 ± 9	$P < 0.001$	28 ± 6	NS	28 ± 6
	P_{Osm}, *mOsm/kg* H_2O	312 ± 4	$P < 0.05$	306 ± 3	NS	306 ± 2

[a] Results are expressed as mean ± SEM ($N = 5$) in each group. The significance of the differences is based on a paired t test.

equal to $[Na^+(o)] \times (R_D/F_W - 1)$ where $[Na^+(o)]$ is the predialysis serum sodium concentration in "molarity" (mEq/liter) measured by flamephotometer, R_D is the Gibbs-Donnan ratio which represents the influence of the negative charge of plasma proteins on ion distribution between serum and dialysate, and F_W is the correction factor for the exclusion volume of plasma proteins. Due to the exclusion volume of plasma protein ($F_W < 1$) serum water Na^+ concentration is $[Na^+(o)]/F_W$ in "molarity" (mEq/kg H_2O), and due to the Gibbs-Donnan effect ($R_D < 1$) the dialysate Na^+ concentration in diffusion equilibrium with serum water across the dialyzer membrane is expressed as $[Na^+(o)] \times R_D/F_W$ in both "molarity" and "molality." Although both R_D and F_W vary as functions of plasma total protein concentration [9, 10], the ratio of R_D/F_W is estimated constant (1.03) over a wide range of total protein concentration from 6.5 to 9.2 g/dl (see the **Appendix**). This figure is entered in our computer program. The non-zero X-intercept indicates that when serum and dialysate are in diffusion equilibrium, the dialysate sodium is slightly (approximately 3%) higher than the serum sodium expressed in "molarity." When the predialysis serum $[Na^+]$ is 140 mEq/liter, the dialysate Na^+ concentration of 144 mEq/liter is in diffusion equilibrium with the serum, and the X-intercept is approximately 4 mEq/liter. For net sodium transfer due to diffusion from dialysate to serum, the Na^+ concentration gradient between dialysate and predialysis serum must exceed the value of the intercept. At gradients lower than the value of the intercept, net sodium transfer from serum to dialysate takes place, resulting in a decrease in serum $[Na^+]$ as observed in both normal and low Na^+ hemodialyses.

Similarly, the influence of the sodium concentration gradient ($\Delta D_{Na}+$) between dialysate and serum (predialysis) on the plasma osmolality change (ΔP_{Osm}) during dialysis is plotted in Figure 2**B**. There was no significant difference between the estimated and measured values. The trend is a linear one, the X-axis intercept being related to the predialysis BUN. The positive intercept indicates such a sodium gradient that the sodium transfer due to diffusion from dialysate to serum prevents the change in P_{Osm} induced by the removal of urea.

The influence of the sodium gradient ($\Delta D_{Na}+$) between dialysate and the predialysis serum concentration on intracellular fluid volume is depicted in Figure 2**C**. Although there was a significant difference ($P < 0.02$) in the patient with low dialysate Na^+ between the estimated and measured values (Table 3), there was no significant difference in the total number of patients. The trend is curvilinear, though the deviation from linearity is small. The intercept on the X-axis is the same as in Figure 2**A**. The intercept represents the sodium gradient between dialysate and serum required to prevent any changes in intracellular volume, the change (ΔECF) in extracellular fluid volume being equal to the amount of fluid removal by ultrafiltration. When higher dialysate Na^+ concentrations beyond this point are used, transcellular fluid shifts out of body cells are predicted by the model, resulting in a change in ECF which would be smaller than the net total body fluid loss. Similarly, with the lower dialysate Na^+ concentrations the transcellular fluid shift will be into body cells, causing a greater decrease in ECF than of total body fluid. As noted, measurements are qualitatively the same as those predicted by the computer with the use of lower dialysate sodium but failed to reach the same magnitude.

Effects of body fluid volume

In these studies, the body fluid volumes were measured using radioisotopes. As this is not feasible in routine clinical practice, we estimated the influence of variations in body fluid volumes on model predictions. The effects of both TBF and the ratio of ICF/ECF on transcellular fluid shifts were negligibly small. There were no effects in the ratio of ICF/ECF on serum $[Na^+]$ and P_{Osm}. Among initial body fluid volumes, therefore, only TBF is important in determination of the postdialysis serum $[Na^+]$ and P_{Osm}. Even with a range of variation in total body fluid volume as large as ±10 liters, the deviations in the postdialysis serum $[Na^+]$ and P_{Osm} were as small as 1.5 mEq/liter and 4 mOsm/kgH_2O, respectively. It is, therefore, evident that a reasonable estimation of the total body water is adequate for clinical application of the computer model, allowing us to predict the postdialysis serum $[Na^+]$ and P_{Osm} and the approximate magnitude of transcellular fluid shifts under given conditions of dialysis.

Discussion

Applying a well established principle [5] governing transcellular fluid dynamics to hemodialysis therapy, a computer-based model [6] has been developed to predict the changes in serum sodium, urea concentration, and osmolality as well as transcellular fluid distribution which occur during hemodialysis. Although we could not verify the validity of the principle in the critical sense, the absolute amount of intracellular effective osmotic cations was kept constant during hemodialysis (Table 2), confirming the clinical validity of application of the principle

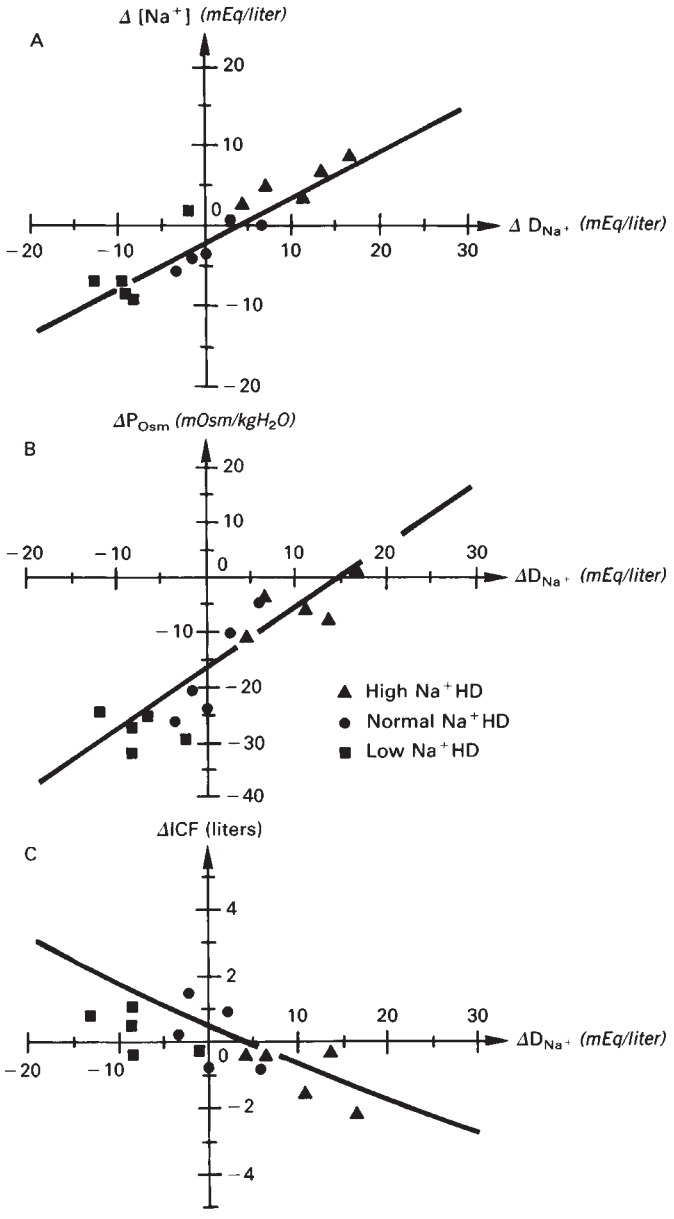

Fig. 2. *Model prediction of the influence of dialysate Na^+ concentration on serum $[Na^+]$* **(A)**, *plasma osmolality* **(B)**, *and transcellular fluid shifts* **(C)**. $\Delta D_{Na}+$ represents the sodium concentration gradient between dialysate and predialysis serum. $\Delta[Na^+]$, ΔP_{Osm}, and ΔICF represent the changes from pre- to postdialysis in serum Na^+ concentration, plasma osmolality, and intracellular fluid volume, respectively. The *plotted points* are the measured values. There was no significant difference between the predicted and measured values in any parameter.

to hemodialysis therapy. Since the present studies were performed in stable chronic hemodialysis patients, however, an application of the principle to unstable or acute hemodialysis patients must be examined further. There can be net flux with a change in the absolute amount of intracellular effective osmotic substances in severely ill patients (for example, severe hypoxia and rapidly developing congestive heart failure) and in the presence of certain pharmacologic agents.

The measurements and model predictions show that serum $[Na^+]$ is decreased and intracellular fluid volume (ICF) is increased during hemodialysis using dialysate Na^+ concentrations lower than those in diffusion equilibrium with predialysis serum. On the other hand, serum $[Na^+]$ is increased and ICF is decreased during hemodialysis using dialysate Na^+ concentrations higher than those concentrations. The equilibrium dialysate Na^+ concentration is considered approximately 3% higher than serum $[Na^+]$ expressed in "molarity" (mEq/liter), indicating that the dialysate Na^+ concentration of 144 mEq/liter is in diffusion equilibrium with the predialysis serum $[Na^+]$ of 140 mEq/liter. Thus, serum $[Na^+]$ was decreased with the increase in ICF when normal Na^+ dialysate (141 ± 2 mEq/liter) containing the same Na^+ concentration as the predialysis serum $[Na^+]$ or low Na^+ dialysate (131 ± 1 mEq/liter) containing 7% less Na^+ concentration than the predialysis serum $[Na^+]$ was used, while serum $[Na^+]$ was increased with the decrease in ICF when dialysate contained 7% higher Na^+ concentration (150 ± 2 mEq/liter) than the predialysis serum $[Na^+]$. The postdialysis values predicted by our model reasonably agree with the measured values except for the changes in body fluid volumes with low Na^+ HD (Table 3). The measured extracellular to intracellular fluid shifts induced by low Na^+ HD were significantly smaller than predicted. One possible explanation for this is that four of the five patients had symptomatic hypotension during low Na^+ HD and received 200 to 700 ml of normal saline. The infusion of normal saline would tend to reduce the fluid shift into cells during low Na^+ HD because of the higher Na^+ concentration in normal saline relative to that in the dialysate used for low Na^+ HD. However, the infusion can explain at most only 0.3 liter of transcellular fluid shifts out of cells.

There are three other mechanisms not considered in our model that could explain the discrepancy in the results with low Na^+ HD. During hemodialysis, because of fluid removal from the vascular compartment, there is an increase in the hematocrit. This hemoconcentration may interfere with Na^+ transport across the dialyzer membrane due to a decrease in the extracorporeal plasma flow rate (see equation *(11)* in the **Appendix**). The resulting decrease in Na^+ dialysance would tend to reduce the fluid shift into cells from the extracellular compartment. As a consequence of vascular refilling and fluid movement into cells the protein concentration increases and the hydrostatic pressure decreases in the interstitium. These changes may have a "braking" effect, in a sense, on the fluid shift into cells by virtue of the resultant imbalance in Starling forces across the cell membrane. Fairly large amounts of potassium, the major intracellular osmotic substance, are removed during hemodialysis [11, 12]. The influence of such removal on transcellular fluid shifts is not considered in the model. The loss of potassium out of cells may decrease ICF due to the decrease in the intracellular effective osmolality. Therefore, potassium flux from the intracellular to the extracellular compartment may also account for the difference between the measured and predicted postdialysis ICF, especially in low Na^+ hemodialysis. In fact, the absolute amount of intracellular effective osmotic cations did decrease during hemodialysis, especially in the patient with low Na^+, although not significant statistically (Table 2).

Good agreement between model predictions and measured values was also noted for the time trend of serum $[Na^+]$ (Fig. 1), and postdialysis values of BUN and P_{Osm} (Table 4). Hence, these results substantiate the clinical validity of the model and

the validity of the underlying assumptions. Having established the clinical validity of the model, we have studied the influence of initial body fluid volumes on the relationships between dialysate Na^+ concentration and serum $[Na^+]$, P_{Osm} or transcellular fluid shifts (Fig. 2). Total body fluid volume (TBF) and the ratio of ICF/ECF were found to have a negligibly small influence on transcellular fluid shifts. No influence of the ratio of ICF/ECF on serum $[Na^+]$ and P_{Osm} was noted. Only the predialysis TBF was found to influence the postdialysis serum $[Na^+]$ and P_{Osm}. When the TBF was altered by ± 10 liters, the changes in serum $[Na^+]$ and P_{Osm} were usually within 1.5 mEq/liter and 4 mOsm/kgH_2O, respectively. Therefore, a rough estimation of the predialysis TBF and the ICF/ECF ratio allows us to predict with reasonable accuracy the postdialysis serum $[Na^+]$, BUN, P_{Osm}, and the change in intracellular volume.

Finally, the model will be useful in the planning of hemodialysis therapy for individual patients when the target values for serum $[Na^+]$, P_{Osm}, and TBF will have been established. The advantages of high Na^+ hemodialysis over normal or low Na^+ hemodialysis in reducing the incidence of hypotension and other symptoms have been reported [1–4]. However, high Na^+ hemodialysis is still not a part of routine clinical practice. A possible reason for this could be the uncertainty in choosing the optimal dialysate Na^+ concentration. The Na^+ concentration should be high enough to reduce the incidence of hypotension and other symptoms and yet not so high as to induce a positive sodium and water balance, resulting in hypertension and pulmonary edema. Using the model, we may be able to select the highest dialysate Na^+ concentration that results in a postdialysis serum $[Na^+]$ within the normal range, thereby minimizing the thirst induced by high Na^+ HD. If the constancy of P_{Osm} during HD is considered important to prevent hypotension and disequilibrium syndrome, the model can prescribe the desired dialysate Na^+ concentration to achieve this. By adjusting the Na^+ dialysance as well as the dialysate Na^+ concentration, we can keep the postdialysis serum $[Na^+]$ within the normal range as well as hold P_{Osm} constant during the treatment. By analyzing transcellular fluid shifts, we can calculate the extent to which the extracellular volume is expanded by high Na^+ HD relative to normal Na^+ or low Na^+ HD. Such a calculation can help us choose rates of fluid removal during the treatment to prevent hypervolemia and the consequent hypertension and pulmonary edema. The model, therefore, provides us with a method for prescribing individualized hemodialysis therapy. By achieving desired values for the postdialysis serum $[Na^+]$ and for body fluid volume at each time of hemodialysis, sodium and water balance can be maintained for a long time.

Appendix

Computer modeling of serum $[Na^+]$, body fluid volumes, and plasma osmolality during hemodialysis

Our computerized model to predict the postdialysis serum $[Na^+]$ and body fluid volumes is based on the following equations [6]. The first one represents the fluid mass balance between intracellular and extracellular compartments.

$$ICF(t + \Delta t) + ECF(t + \Delta t) = ICF(t) + ECF(t) - Q_F \times \Delta t \quad (1)$$

This equation basically states that the change in the combined volume of intracellular (ICF) and extracellular (ECF) fluid compartments from time t to t + Δt is equal to the net fluid removal, where Q_F is the rate of ultrafiltration. The terms (t) and (t + Δt) are used as the arguments of the functions, ICF and ECF, and of other functions in later equations, and X (t) and X (t + Δt) mean X at time t and t + Δt, respectively.

The second equation is the mass conservation relationship for the sum total of effective osmotic substances in the cell which do not penetrate the cell membrane.

$$ICF(t + \Delta t) \times C_I(t + \Delta t) = ICF(t) \times C_I(t) \quad (2)$$

This equation states that the sum total of effective osmotic substances in the cell is unchanged, changes in concentration being related to fluid shifts across the cell membrane. Here, $C_I(t)$ is the effective osmolality within the cell, and should be equal to that in extracellular fluid, $C_E(t)$, because of osmotic equilibrium across the cell membrane.

$$C_I(t) = C_E(t) \quad (3)$$

The effective osmolalities, $C_I(t)$ and $C_E(t)$, are the quantitative indices of the chemical potential of water, and this equation means that the chemical potential of water is the same inside every cell as it is in interstitial fluid. As the extracellular effective osmolality changes, a transcellular fluid shift will occur until the effective osmolality in both the extracellular and intracellular compartments reaches equilibrium, resulting in a change in the ICF.

The next equation is the mass balance relationship for the sum total of effective osmotic substances in the extracellular fluid.

$$ECF(t + \Delta t) \times C_E(t + \Delta t) - ECF(t) \times C_E(t) = \text{Dialysance} \times \Delta t \times \{C_D - C_E(t)\} - Q_F \times \Delta t \times C_E(t) \quad (4)$$

Here, Dialysance is defined as the minute rate of net exchange by diffusion between blood and dialysate per unit dialysate − blood concentration gradient, and C_D is the effective osmolality in the dialysate. Since it is assumed that these substances do not enter the cell across the cell membrane, the equation indicates that the changes in ECF of these substances reflects net exchange by diffusion and removal by ultrafiltration. Dialysance × Δt × $\{C_D - C_E(t)\}$ represents net exchange of effective osmotic substance between dialysate and extracellular fluid by diffusion during the time interval between t and (t + Δt), and $-Q_F \times \Delta t \times C_E(t)$ is net exchange by way of ultrafiltration, where the + direction represents gain by the extracellular fluid.

In the above modeling, only Na^+ and its accompanying anions are considered important as effective osmotic substances in extracellular fluid, the cell membrane being assumed to be freely permeable to urea. Therefore, there is a relationship between effective osmolarity, $C_E(t)$, in extracellular fluid and serum $[Na^+(t)]$.

$$C_E(t) = k \times [Na^+(t)] \times \frac{R_D}{F_W} \quad (5)$$

where k is the osmotic coefficient for sodium chloride that converts concentration to osmolality, R_D is the Gibbs-Donnan ratio for Na^+, and F_W is the plasma water fraction. This equation is an expression of total density of solute affecting the colligative properties of the aqueous solution, in terms of the

measured concentration of Na^+ in serum. It corrects for serum water fraction, for the Gibbs-Donnan equilibrium ratio, and for the activity coefficient of sodium chloride. The sodium concentration in interstitial fluid, $[Na^+(t)] \times R_D/F_W$ also corresponds to the dialysate Na^+ concentration when serum and dialysate are in diffusion equilibrium across the dialyzer membrane. Similarly, there is a relationship between effective osmolality, C_D, in the dialysate and dialysate Na^+ concentration, $[Na^+]_D$.

$$C_D = k \times [Na^+]_D \quad (6)$$

Since k appears on both sides of equations *(2)* and *(4)* after substituting $C_I(t)$ and $C_E(t)$ by equation *(5)* and C_D by equation *(6)*, it factors out. Although both R_D and F_W vary as functions of total protein concentration, T_P (g/dl), in plasma [9, 10], the ratio of R_D/F_W is estimated constant (1.03) over a wide range of total protein concentrations from 6.5 to 9.2 g/dl.

$$R_D = 1.004 \times EXP(-0.008 \times T_P) \quad (7)$$

$$F_W = 1 - 0.0107 \times T_P \quad (8)$$

$$R_D/F_W = 1.03 \qquad (6.5 \leqq T_P \leqq 9.2) \quad (9)$$

In addition to modeling serum $[Na^+]$ and body fluid volume, changes in blood urea nitrogen concentration (BUN) during hemodialysis were also modeled. As urea is assumed to move freely across the cell membrane and to be distributed uniformly within total body water, the mass conservation relationship for urea yields:

$$TBF(t \times \Delta t) \times \frac{BUN(t + \Delta t)}{F_W} - TBF(t) \times \frac{BUN(t)}{F_W}$$

$$= G_U \times \Delta t - (Clearance + Q_F) \times \Delta t \times \frac{BUN(t)}{F_W} \quad (10)$$

where TBF is the total body fluid voume, G_U is the urea nitrogen generation rate (assumed to be 7 mg/min for stable patients), and F_W is the plasma water fraction which was assumed to be 0.925. The Na^+ dialysance and urea clearance were corrected for the influence of ultrafiltration on the plasma or blood flow rates within the dialyzer as follows [13]:

$$Na^+ \text{ dialysance} = K_{urea} \times \left(1 - \frac{Q_F}{Q_P}\right) \quad (11)$$

$$\text{Urea clearance} = K_{urea} \times \left(1 - \frac{Q_F}{Q_B}\right) \quad (12)$$

Where the Na^+ dialysance was assumed equal to the urea clearance when $Q_F = O$, K_{urea} is the dialyzer urea clearance measured at a zero ultrafiltration rate, and Q_P is the extracorporeal plasma flow rate calculated as $Q_B \times (1 - Hct/100)$.

The change in plasma osmolality (P_{Osm}) during hemodialysis was calculated assuming that it occurs due to the changes in serum $[Na^+]$ and BUN.

$$P_{Osm}(t + \Delta t) - P_{Osm}(t) = \frac{k}{F_W} \times \{[Na^+(t + \Delta t)] -$$

$$[Na^+(t)]\} + \frac{1}{2.8 \times F_W} \{BUN(t + \Delta t) - BUN(t)\} \quad (13)$$

The osmotic coefficient k referred to earlier was assumed to be 1.9 for sodium chloride.

Solving equations *(1)* to *(6)*, *(9)* and *(11)*, $[Na^+(t + \Delta t)]$, $ICF(t + \Delta t)$, and $ECF(t + \Delta t)$ can be expressed in terms of $[Na^+(t)]$, ICF(t), and ECF(t). If the initial conditions, $[Na^+(o)]$, ICF(o) and ECF(o), are known, $[Na^+(\Delta t)]$, $ICF(\Delta t)$, and $ECF(\Delta t)$ can be calculated. Repeating this process in steps of Δt using a computer (9845S, Hewlett-Packard, Elkhart, Indiana), $[Na^+(t)]$, ICF(t), and ECF(t) at finitely spaced points in time during hemodialysis are obtained. Similarly, BUN(t) and $P_{Osm}(t)$ can then be calculated using equations *(10)*, *(12)*, and *(13)*. These parameters were calculated at intervals of 1 min ($\Delta t = 1$), but no differences were seen with Δt in a range of 0.1 to 5.0 min.

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